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# $ACP_1$ and $ADA_1$ Genetic Polymorphisms and Coronary Artery Disease. Effects on Age at Onset of Clinical Manifestations

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## Abstract

Previous studies have shown an association of Coronary Artery Disease (CAD) with Acid Phosphatase locus 1 ($ACP_1$) and Adenosine Deaminase locus 1 ($ADA_1$) genetic polymorphisms. Both systems are involved in immune reactions and several studies point to a significant autoimmune component in the pathogenesis of CAD. In the present note we have investigated the role of the two polymorphisms on age of onset of the disease.

Hundred and thirty patients admitted to Valmontone Hospital for the first episode of CAD have been studied. Informed consent was obtained by the patients to participate in the study that was approved by the Sanitary Direction of the Hospital.

In patients at the first episode of CAD, $ACP_1$ genotype was determined in 130 subjects and $ADA_1$ genotype in 126 subjects by DNA analysis. SPSS programs performed statistical analyses.

The age at onset of CAD is lower in subjects with low $ACP_1$ activity genotypes and in those with low $ADA_1$ activity genotypes. The association is stronger in females than in males. The effects of the two systems appears additive with a lower age of onset in subjects carrying the two factors associated with lower age at onset and a higher age in subjects with no factor. The pattern is stronger in females than in males.

Gender differences in autoimmunity are well documented: women with low $ACP_1$ activity and/or $ADA_1$ genotype seem to have a high risk of early clinical manifestations as compared to women carrying genotypes with high activity. These differences support the hypothesis of significant autoimmune component in the pathogenesis of CAD.

**Keywords**:

$ACP_1$; $ADA_1$; CAD; Age at onset

## Introduction

Previous studies have shown an association of Coronary Artery Disease (CAD) with Acid Phosphatase locus 1 ($ACP_1$) [1] and with Adenosine Deaminase ($ADA_1$) [2,3]. The present analysis suggests an effect of these genetic systems on the age at onset of clinical manifestations of the disease.

$ACP_1$ gene is located on chromosome 2 and encodes the Low Molecular Weight Protein Tyrosine Phosphatase (LMWPTP). The gene shows three co dominant alleles *A, *B and *C: the corresponding 6 genotypes show an activity increasing in the order *A/*A<*A/*B<*B/*B≤ *A/*C<*B/*C<*C/*C. The enzyme has several functions: (i) as flavin mononucleotide phosphatase catalyzes the conversion of flavin mononucleotide to riboflavin contributing to the regulation of flavo-enzymes activity and energy metabolism; (ii) dephosphorylating insulin receptor and band 3 protein modulates the glycolytic rate; (iii) dephosphorylating a negative regulatory Tyr-292 of ZAP-70, $ACP_1$ strengthens T cell receptor signaling [4,5].

| Parameter | % Proportion |
|---|---|
| Infarction | 40.5% |
| Major Coronary Lesions | 83.2% |
| Bypass | 35.2% |
| Angioplasty | 27.1% |

**Table 1:**Clinical data in subjects with CAD

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| | All subjects | | | Females | | | Males | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean age | S.E. | n° (yrs) | Mean age | S.E. | n° (yrs) | Mean age | S.E. | n° (yrs) |
| $ACP_1$ | | | | | | | | | |
| Low activity genotypes (*A/*A and *A/*B) (A) | 63.10 | 1.85 | 51 | 61.26 | 2.49 | 23 | 64.61 | 2.69 | 28 |
| Medium activity genotype (*B/*B) (B) | 67.00 | 1.36 | 59 | 68.53 | 2.62 | 19 | 66.8 | 1.59 | 40 |
| High activity genotypes (*A/*C, *B/*C and *C/*C) (C) | 69.45 | 2.70 | 20 | 69.67 | 3.87 | 13 | 68.86 | 3.22 | 7 |
| Statistical analysis A vs B vs C linear correlation p=0.027 eta =0.197 eta squared=0.040 A vs (B+C) difference between means p=0.036 eta=0.185 eta squared=0.040 | | | | A vs B vs C linear correlation p = 0.034 eta= 0.310 eta squared=0.095 A vs (B+C) difference between means p=0.023 | | | A vs B vs C linear correlation p=0.371 eta=0.107 eta squared=0.011 A vs (B+C) difference between means p=0.860 | | |
| $ADA_1$ | | | | | | | | | |
| Low activity genotypes (carriers of $ADA_1$*2 allele) | 59.21 | 3.55 | 14 | 55.38 | 4.71 | 8 | 64.33 | 5.09 | 6 |
| High activity genotypes ($ADA_1$ *1/*1 genotype) | 66.72 | 1.11 | 112 | 67.31 | 1.78 | 45 | 66.33 | 1.42 | 67 |
| Statistical analysis difference between means p=0.028 eta=0.146 eta squared=0.040 | | | | difference between means p=0.013 eta=0.338 eta squared=0.114 | | | difference between means p=0.690 eta=0.047 eta squared=0.002 | | |

**Table 2:** Age at onset of CAD in relation to $ACP_1$ and $ADA_1$ genetic polymorphisms

Several studies point to a significant link between atherosclerosis and the genetics of autoimmunity. $ACP_1$ has been found associated with several immune diseases including Coronary Artery Disease (CAD) suggesting an important relationship between this polymorphism and CAD possibly through the relationship of $ACP_1$ with ZAP70.

The ADA gene is located on chromosome 20 and it is constituted by 12 exons. A number of single nucleotide polymorphisms have been found within the coding and intronic regions of the gene [6]. The SNP ($ADA_1$) corresponding to the presence /absence of a Taq I site (4050-4053 exon 1, C22 G > A, Asp8Asn, rs 73598374) has been found associated with CAD [2,3]. This SNP at exon 1 corresponds to a known functional variant since the G > A transition results in the substitution of asparagine for aspartic acid at codon 8. This mutation is the molecular basis for the biochemical polymorphism at the $ADA_1$ locus described by Spencer et al., with two codominant alleles with activity decreasing in the order $ADA_1$*1 > $ADA_1$*2 [7].

$ADA_1$ catalyzes the irreversible deamination of adenosine to inosine contributing with adenosine kinase to the intra and extra-cellular concentration of adenosine. Carriers of $ADA_1$*2 allele show a low enzymatic activity as compared to $ADA_1$ *1/*1 genotype. Adenosine has an important role in glucose metabolism and immune functions and is a cardio-protective agent [8,9].

## Material and Methods

We have studied 130 patients admitted to Valmontone Hospital for the first episode of Coronary Artery Disease. 55 were females and 75 males. Part of these subjects have been included in previous studies [1,3]. Informed consent was obtained from the patients to participate to the study that was approved by the Sanitary Direction of the Hospital. Clinical data of subjects examined are shown in table 1.

$ACP_1$ genotype was determined in 130 subjects admitted in the Hospital for the first episode of CAD. $ADA_1$ genotype was determined in 126 subjects at first episode. $ACP_1$ and $ADA_1$ genotypes were determined by DNA analysis as previously described. [1,3].

Statistical analyses were carried out by commercial software (SPSS). Eta (η) is a measure of association and eta squared ($\eta^2$) represents the proportion of variance of dependent variable that is explained by the independent variable.

## Results

Table 2 shows the age of subjects admitted to the Hospital for the first episode of CAD in relation to the genotypes of $ACP_1$ and $ADA_1$. The age at onset of clinical manifestations is lower in subjects with low $ACP_1$ activity as compared to other $ACP_1$ genotypes and in carriers of $ADA_1$ *2 allele (associated with lower ADA enzymatic activity) as compared to $ADA_1$ *1/*1 genotype. Although the pattern appears similar in males and females, it is stronger in females than in males. For $ACP_1$ eta is 0.308 in females and 0.107 in males. For $ADA_1$ eta is 0.338 in females and 0.047 in males.

As shown in table 3 the effect of the two genotypes in subjects admitted to the Hospital for the first episode of CAD appears additive with a lowest age in subjects carrying the two factors associated with lower age at onset and the highest age in subjects with no factor. Although the pattern is similar in males and females, it is much stronger in females than in males. In females eta is 0.456, eta squared is 0.208 while in males eta is 0.185 and eta squared is 0.034.

We have considered in females the effect of the following variables: hypertension, obesity and diabetes. No statistically significant effect of these variables was observed neither on the difference between low activity and medium-high activity $ACP_1$ genotypes nor on the difference between low activity $ADA_1$ genotypes and high activity $ADA_1$ genotype.

| | All subjects | | | Females | | | Males | | |
|---|---|---|---|---|---|---|---|---|---|
| Number of factors | Mean age at onset (yrs) | S.E. | n° | Mean age at onset (yrs) | S.E. | n° | Mean age at onset (yrs) | S.E. | n° |
| 0 | 68.35 | 1.26 | 69 | 71.15 | 2.14 | 27 | 66.55 | 1.51 | 42 |
| 1 | 63.88 | 1.69 | 57 | 61.68 | 2.30 | 25 | 65.59 | 2.39 | 32 |
| 2 | 50.75 | 6.32 | 4 | 51.67 | 8.84 | 3 | 48.00 | - | 1 |
| Statistical analysis<br>linear correlation p=0.002<br>eta =0.290 eta squared=0.084 | | | | linear correlation p=0.001<br>eta=0.456 eta squared=0.208 | | | linear correlation p=0.390<br>eta=0.185 eta squared=0.034 | | |

**Table 3:** The relationship between age at onset of clinical manifestations of CAD and the number of genetic factors for which an earlier onset of manifestation has been observed.

## Discussion

The present analysis shows a statistically significant positive correlation between $ACP_1$ activity and age at onset of CAD: low activity $ACP_1$ genotypes are associated with early onset of clinical manifestations while high activity genotypes are associated with late onset of manifestations. Such correlation is statistically significant in females but not in males. Since low $ACP_1$ activity is associated in females to early onset and probably to early mortality also, this could result in an apparent relative increase of $ACP_1$ genotypes with high activity in the surviving subjects with CAD. The data also indicate that $ADA_1$ *2 allele is associated in females to early onset of clinical manifestations and probably to early mortality. This could result in an apparent relative decrease of subjects carrying this allele in surviving subjects [1,2].

The analysis confirms the involvement of $ACP_1$ and $ADA_1$ in the risk of CAD and suggests an additive effect of the two systems on age at onset of the disease.

Several studies point to a significant autoimmune component in the pathogenesis of atherosclerosis [10,11]: gender differences in autoimmunity are well documented and it has been suggested that in diseases with autoimmune component males and females should be examined separately [12].

The limitation of the study is represented by the relatively low number of subjects examined and by the lack of information on the distribution of $ACP_1$ and $ADA_1$ in subjects not surviving the first episode of CAD.

From the practical point of view the determination of $ACP_1$ and $ADA_1$ genotypes may help to detect subjects with high risk of early manifestations of CAD

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